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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/613,749	07/03/2003	Arthur M. Krieg	C01037.70041.US	6452

23628 7590 05/09/2005

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BOSTON, MA 02210-2211

EXAMINER	
MINNIFIELD, NITA M	

ART UNIT	PAPER NUMBER
1645	

DATE MAILED: 05/09/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/613,749	KRIEG, ARTHUR M.	
	Examiner	Art Unit	
	N. M. Minnifield	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 4 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 February 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *See Continuation Sheet* is/are pending in the application.

4a) Of the above claim(s) *See Continuation Sheet* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,8-12,14,17-21,23,28-33 and 44* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *See Continuation Sheet* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *03 July 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892) 8 sheets

2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 10/27/04; 4/29/04 3 sheets

4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.

5) ☐ Notice of Informal Patent Application (PTO-152)

6) ☐ Other: _____.

Continuation of Disposition of Claims: Claims pending in the application are 1-15,17-21,23,28-33,44,46-58,64-66,71-74,77-81,84,85,89,90,95,96 and 98.
Continuation of Disposition of Claims: Claims withdrawn from consideration are 5-7,13,15,46-58,64-66,71-74,77-81,84,85,89,90,95,96 and 98.

Continuation of Disposition of Claims: Claims subject to restriction and/or election requirement are 5-7, 13, 15, 46-58,64-66,71-74,77-81,84,85,89,90,95,96 and 98.

DETAILED ACTION

1. Applicant's amendment filed February 10, 2005 is acknowledged and has been entered. Claims 16, 22, 24-27, 34-43, 45, 59-63, 67-70, 75, 76, 82, 83, 86-88, 91-94, 97 and 99 have been canceled. Claims 12, 46 and 98 have been amended. Claims 1-15, 17-21, 23, 28-33, 44, 46-58, 64-66, 71-74, 77-81, 84, 85, 89, 90, 95, 96 and 98 are now pending in the present application.

2. Applicant's election with traverse of Group I, claims 1-4, 8-12, 14, 17-21, 23, 28-33 and 44 (elected species of cancer antigen and chemotherapeutic agent) in the reply filed on December 27, 2004 is acknowledged. The traversal is on the grounds that restriction of Groups I and II and Groups I and III should be rejoined. Applicant asserts that the Examiner has not met the burden under MPEP 806.05(h) of providing examples of an alternative viable use for the composition of claim 1 or an alternative viable product to be used in claims 46 and 98. However, Groups I and III are distinct because the process of using (group III) the claimed product (group I) can be practiced with another materially different product. The method of stimulating an immune response in a subject can be achieved by administering antigen, such as HBsAg or a bacterial antigen. The product of group I as claimed can be used in a materially different process; for example the method of identifying an immunostimulatory compound as set forth in canceled claim 99.

Applicant asserts that the product of claim 1 is the same as that recited in claims 46 and 98, and in the interest of expediting prosecution, Applicant herewith amends claims 46 and 98 to depend from claim 1. Accordingly, there is no basis for at least the position that the process of using can be practiced with another

materially different product. Applicant further points out that, even if claims are distinct, there must still be a serious burden on the Examiner in order to justify their restriction. Applicant maintains that no serious burden exists, since the common element in the claims of Groups I and III is the immunostimulatory nucleic acid comprising a nucleotide sequence of SEQ ID NO: 1. Applicant further requests rejoinder of Groups I and III under MPEP 821.04.

With regard to serious burden, the restriction Groups have acquired a separate status in the art as a separate subject for inventive effect and require independent searches. The search for each of the above inventions is not co-extensive particularly with regard to the literature search. A reference, which would anticipate the invention of one group would not necessarily anticipate or make obvious any of the other groups. Moreover, as to the question of burden of search, classification of subject matter is merely one indication of the burdensome nature of the search involved. The literature search, particularly relevant in this art, is not co-extensive and is much more important in evaluating the burden of search. Burden in examining materially different groups having materially different issues also exist.

The examiner has required restriction between product and process claims. Where applicant elects claims directed to the product, and a product claim is subsequently found allowable, withdrawn process claims that depend from or otherwise include all the limitations of the allowable product claim will be rejoined in accordance with the provisions of MPEP § 821.04. **Process claims that depend from or otherwise include all the limitations of the patentable product** will be entered as a matter of right if the amendment is presented prior to final rejection or allowance,

whichever is earlier. Amendments submitted after final rejection are governed by 37 CFR 1.116; amendments submitted after allowance are governed by 37 CFR 1.312.

In the event of rejoinder, the requirement for restriction between the product claims and the rejoined process claims will be withdrawn, and the rejoined process claims will be fully examined for patentability in accordance with 37 CFR 1.104. Thus, to be allowable, the rejoined claims must meet all criteria for patentability including the requirements of 35 U.S.C. 101, 102, 103, and 112. Until an elected product claim is found allowable, an otherwise proper restriction requirement between product claims and process claims may be maintained. Withdrawn process claims that are not commensurate in scope with an allowed product claim will not be rejoined. See "Guidance on Treatment of Product and Process Claims in light of *In re Ochiai, In re Brouwer* and 35 U.S.C. § 103(b)," 1184 O.G. 86 (March 26, 1996). Additionally, in order to retain the right to rejoinder in accordance with the above policy, Applicant is advised that the process claims should be amended during prosecution either to maintain dependency on the product claims or to otherwise include the limitations of the product claims. **Failure to do so may result in a loss of the right to rejoinder.**

Further, note that the prohibition against double patenting rejections of 35 U.S.C. 121 does not apply where the restriction requirement is withdrawn by the examiner before the patent issues. See MPEP § 804.01.

Group III will be rejoined with Group I once the claims of Group I have been deemed allowable.

Applicant further traverses the Restriction on the basis that there is no serious burden on the Examiner to consider Groups I and II together under MPEP

808.02. The Examiner has classified both Groups in class 536. The Examiner has provided no evidence for the separate status of Groups I and II in the art, and a search of Group I is expected to identify art relevant to Group II and vice versa, particularly since the common element of Groups I and II is an immunostimulatory nucleic acid comprising a nucleotide sequence of SEQ ID NO: 1. However, the product of Group I is a composition comprising the immunostimulatory nucleic acid molecule and an antigen. Group II is a composition comprising the immunostimulatory nucleic acid molecule and the antigen is encoded by a nucleic acid vector, further the vector is separate from the immunostimulatory nucleic acid molecule. Group II encompasses DNA vaccines and gene therapy, which is distinct from the compositions of Group I. The two inventions have different modes of action and function when administered to asubject.

Applicant's arguments have been considered and are not found persuasive for the reasons set forth above. The requirement is still deemed proper and is therefore made FINAL.

3. Claims 5-7, 13, 15, 46-58, 64-66, 71-74, 77-81, 84, 85, 89, 90, 95, 96 and 98 have withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention and/or species, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on December 27, 2004.

4. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude"

granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

5. Claims 1, 3, 8-10, 17, 18, 20, 21, 23 and 30-33 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 41-46, 52-56 and 58 of copending Application No. 10/816220 (2004/0076905). Although the conflicting claims are not identical, they are not patentably distinct from each other because both applications claim compositions comprising an immunostimulatory nucleic acid molecule, an antigen and optionally an adjuvant. Application 10/613749 claims SEQ ID NO: 1 and Application 10/816220 claims SEQ ID NO: 148; these sequences are the same.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

6. The Examiner has considered the information disclosure statement (IDS) submitted on April 29, 2004, October 27, 2004 and March 21, 2005. There was no Form PTO-1449 submitted on March 21, 2005, only the IPER for PCT/US03/21113.

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

8. Claims 1 and 23 are rejected under 35 U.S.C. 102(a) as being anticipated by Olek et al (WO 2002/18632 or WO 2001/92565).

Claims 1 and 23 are directed to a composition comprising an immunostimulatory nucleic acid molecule comprising the nucleotide sequence of SEQ ID NO: 1, and that the immunostimulatory nucleic acid molecule includes at least four CpG motifs.

Olek et al, WO 2002/18632, discloses a composition comprising the nucleotide sequences (claims; abstract). SEQ ID NO: 4789, 4790, 19850, 19849 and 5396 comprise Applicant's claimed SEQ ID NO: 1 (please see the attached sequence search result print out). The prior art sequences have at least four CpG motifs.

Olek et al, WO 2001/92565, discloses a composition comprising the nucleotide sequences (claims; abstract). SEQ ID NO: 244 comprises Applicant's claimed SEQ ID NO: 1 (please see the attached sequence search result print out). The prior art sequence has at least four CpG motifs.

Since the Patent Office does not have the facilities for examining and comparing applicants' composition with the composition of the prior art reference, the burden is upon applicants to show a distinction between the material structural and functional characteristics of the claimed composition and the composition of the prior art. See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and In re Fitzgerald et al., 205 USPQ 594.

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 1-4, 8-12, 14, 17-21, 23, 28-33 and 44 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a composition comprising SEQ ID NO: 1 and an antigen (HbsAg) and its use, does not reasonably provide enablement for a composition comprising SEQ ID NO: 1, a cancer antigen and chemotherapeutic agent and the use of the composition. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The specification teaches a composition comprising SEQ ID NO: 1 (ODN 10102) and HBsAg, and that this composition was used to immunize mice (see pp. 85-89).

The specification is not enabled for the use of a composition comprising SEQ ID NO: 1 and a cancer antigen or a composition comprising SEQ ID NO: 1, a cancer antigen and a chemotherapeutic agent. The specification teaches how to

make the composition, however the use of the composition is not enabled. The detailed description of the invention at pp. 24-29, pp. 43-44, pp. 59-62 and pp. 65-67 describes the various aspects of cancer and how the composition *could be* used and p. 49 indicates that CpG is useful as a vaccine adjuvant. Table 2 provides numerous examples of cancer immunotherapies that are currently being used or are in development (see pp. 62-65). Table 3 provides a list of a variety of cancer vaccines that are currently being used or are in development (see pp. 67-68) and Table 4 provides a list of chemotherapeutic agents that are currently in development or in use in a clinical setting (see pp. 69-71). The use of the composition would be for treatment in cancer in view of the descriptions in the specification. The recitation of cancer antigen encompasses any and all cancers and tumors. The specification does not teach an example of the use of the claimed composition in the treatment of any cancer or cancer therapies in a subject. The specification does not provide any indication as to which of the many cancer immunotherapies for the numerous cancers cited in Table 2 have benefited from the administration of the claimed composition being a part of the subject's cancer treatment or cancer therapy. The same for the many cancer vaccines and chemotherapeutic agents listed in Tables 3 and 4 respectively.

The state of the art with regard to cancer therapy is unpredictable, in addition CpG immunostimulatory nucleic acid molecules in cancer therapy is unpredictable. Donnelly et al (Nature Medicine, 2003, 9/11:1354-1356) teaches that over many decades various approaches to eliciting both innate and acquired immune responses against tumors have been tried, some with a degree of success. However, immunotherapy has yet to be incorporated into first-line therapies for more than a very few types of cancers such as the use of IL-2 immunotherapy for

metastatic renal cell carcinoma (p. 1354, col. 2). Further, Donnelly teaches that treating cancer with something that looks more like a modern-day vaccine, with a defined antigen and an optimized adjuvant and delivery platform, is still in the future (see p. 1354, col. 2; see also col. 3). "A variety of anti-tumor vaccine clinical trials have been undertaken. In spite of the large number of these trials, and the plethora of distinct approaches investigated, there has been little evidence of clinical efficacy. Furthermore, precise correlates of clinical effects and immunological responses have been lacking." (DeGruijl et al, Nature Medicine, 1999, 5/10:1124-1125, see p. 1124, col. 1) Bitton R. J. (Current Opinion in Molecular Therapeutics, 2004, 6/1:17-25) teaches that developing cancer vaccines to treat solid tumors is not an easy task (abstract). Bitton teaches that "immune editing" , in part, explains why many cancer vaccines work in animal models but not in a clinical setting (abstract). Bitton describes the various cancer vaccine strategies and evaluates the evidence supporting their efficacy (abstract). Bitton indicates that the final picture with regard to cancer vaccines is confusing and comparison of different vaccine strategies is almost impossible because of the different strategies from different groups. Further, most of the vaccines are still experimental, far from being approved by regulatory authorities and their clinical utility is almost negligible (abstract). Bitton teaches that therapeutic vaccines have proved to have little use in cancer treatment and that in fact in almost every well-designed, well-controlled, randomized phase III trial, they have failed to demonstrate any significant improvement in overall or disease-free survival (p. 17, col. 2; Table 2). "It is clear that most vaccines are indeed effective immunogens, but they do not seem to be effective at triggering anticancer responses. Tumor size reduction, the classic endpoint in clinical development of cytotoxic drugs does not

seem to be useful in evaluating cancer vaccines; tumor stabilization might be more valuable. Finally, there is no evidence of improvement in overall survival or disease-free survival. The implementation of well-designed randomized phase III trials is urgently required." (pp. 24-25)

With regard to CpG in the treatment of cancers, Weiner indicates that there is therapeutic potential in cancer treatment for CpG as an immune adjuvant (Table 1) and that there are a number of scenarios where CpG could be used as a component of cancer immunotherapy, each of these areas is under intensive investigation (p. 458, col. 1). Studies in a tumor model (38C13 murine lymphoma) indicate that CpG was just as effective as CFA at inducing an antigen-specific antibody response (p. 458, col. 2). Weiner teaches that "[P]reliminary studies suggest CpG ODN can be effective in a variety of scenarios when used alone or in combination with other agents. Despite this promise we still do not understand the molecular mechanisms responsible for the immunostimulatory effects of CpG ODN. All CpG ODN are not alike, and more needs to be learned about the heterogeneous responses that occur based on host organism, cell subset, or CpG ODN sequence. Most importantly, we have not yet explored their clinical effects. Further work with CpG ODN in both the laboratory and the clinic is needed before we can know their true promise as investigational immunological and therapeutic agents." (p. 461, col. 1) Krieg et al teaches that CpG has NK-stimulating properties and suggest that it can be used in immunotherapy of tumors, yet Krieg et al also indicates that many or even most types of tumors are relatively resistant to NK-mediated lysis (p. 117, col. 2). Ballas et al teaches that the selection of optimal CpG ODN for cancer immunotherapy depends upon a careful analysis of the cellular specificities of various CpG motifs and an understanding of the cellular

mechanisms responsible for the antitumor activity in a particular tumor (abstract). Ballas et al teaches that a single CpG ODN can not be used to treat all cancers and tumors. Although several CpG ODN were active as sole immunotherapeutic agents in two tumor models, different motifs were optimal in each model. CpG ODN 1585 was optimal against B16 melanoma and its effects were dependent on NK cells. CpG ODN 1826 was optimal in a lymphoma model and its effects appeared to require NK (early) and T cells (late). These results illustrate that the potent distinct CpG motifs can be custom-tailored for each desired immune effect (p. 4878, col. 2; see also p. 4885, col. 1). Agrawal et al (TRENDS in Molecular Medicine, 2002, 8/3:114-120) also teaches that different effects are observed with different CpG ODNs.

In view of the fact that there are so many different cancer vaccines, immunotherapies and chemotherapeutic agents being used or developed for the treatment of the myriad of cancers and tumors; and the fact that CpG ODN has only been shown to useful in one or two tumor animal models, but does not show the same type of results in clinical trials, it would require undue experimentation for a skilled artisan to practice the claimed invention. The state of the art is unpredictable with regard to both cancer therapies and the use and number of different CpG ODN. Applicant's specification does not set forth any enablement using SEQ ID NO: 1 in a composition (alone or with a cancer antigen) in a cancer treatment or cancer immunotherapy. The art teaches that there are no established clinical protocols for effective cancer therapies. There would be undue experimentation required to practice the claimed methods with a reasonable expectation of success of the claimed composition being successful in cancer treatment or cancer therapies, absent a specific and detailed description in

applicant's specification of how to effectively use the claimed compositions and absent working examples providing evidence which is reasonably predictive of the use of the claimed composition for use in cancer therapies for the myriad of known cancers and/or tumors.

11. No claims are allowed.

12. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to N. M. Minnifield whose telephone number is 703-305-3394. The examiner can normally be reached on M-F (8:00-5:30) Second Friday Off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette R.F. Smith can be reached on 703-308-3909. The fax phone number for the organization where this application or proceeding is assigned is 703-308-4556.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

N. M. Minnifield
Primary Examiner
Art Unit 1645

NMM

April 25, 2005

Please mail 4 Office Actn 4/25/05 rm

PS Claim 4; SEQ ID NO 36; 276pp; English.
XX
CC The invention relates to an immunostimulatory nucleic acid molecule
CC comprising an internal pyrimidine-purine (YZ) dinucleotide and chimeric
CC backbone, where one internal YZ dinucleotide has a phosphodiester(-like)
CC internucleotide linkage, where optionally each additional internal YZ
CC dinucleotide has a phosphodiester(-like) or stabilised internucleotide
CC linkage, where other internucleotide linkages are stabilised. The
CC oligonucleotide is useful in stimulating or modulating an immune
CC response. The medicament shifts the immune response to a Th1 biased
CC response from a Th2 biased response. The oligonucleotide is also useful
CC in the manufacture of a medicament for treating asthma, allergy, cancer,
CC infectious disease, autoimmune disease, airway remodeling or chronic
CC obstructive pulmonary disease or in treating a subject who is a smoker or
CC who is free of symptoms of asthma. The oligonucleotide is useful in
CC inducing cytokine expression, e.g. IL-6 (interleukin-6), TNFalpha (tumour
CC necrosis factor alpha), IFNalpha (interferon-alpha), IFNgamma (interferon
CC -gamma) and IP-10 (interferon inducible protein). The oligonucleotide is
CC also useful in treating and preventing infections caused by viruses,
CC bacteria and parasites. The present sequence represents an
CC immunostimulatory nucleic acid.
XX
SQ Sequence 24 BP; 0 A; 6 C; 6 G; 12 T; 0 U; 0 Other;

Query Match 100.0%; Score 24; DB 12; Length 24;
Best Local Similarity 100.0%; Pred. No. 0.74;
Matches 24; Conservative 0; Mismatches 0; Indels 0; Gaps 0;

Qy 1 TCGTCGTTTCGTCGTTTCGTCGTT 24
||||||||||||||||||||||||
Db 1 TCGTCGTTTCGTCGTTTCGTCGTT 24

RESULT 4
ADK19223
ID ADK19223 standard; DNA; 24 BP.
XX
AC ADK19223;
XX
DT 20-MAY-2004 (first entry)
XX
DE Immunostimulatory nucleic acid #269.
XX
KW immunostimulatory nucleic acid; asthma; allergy; cancer;
KW infectious disease; autoimmune disease; airway remodeling;
KW chronic obstructive pulmonary disease; asthma; IL-6; interleukin-6;
KW TNFalpha; tumour necrosis factor alpha; IFNalpha; interferon-alpha;
KW IFNgamma; interferon-gamma; IP-10; interferon inducible protein;
KW viral infection; bacteria infection; parasitic infection; ss.
XX
OS Synthetic.
XX
PN WO2004016805-A2.
XX
PD 26-FEB-2004.
XX
PF 19-AUG-2003; 2003WO-US025935.
XX
PR 19-AUG-2002; 2002US-0404479P.
PR 19-AUG-2002; 2002US-0404820P.
PR 27-NOV-2002; 2002US-0429701P.
PR 14-FEB-2003; 2003US-0447377P.
XX
PA (COLE-) COLEY PHARM GROUP INC.
PA (COLE-) COLEY PHARM GMBH.
XX
PI Krieg AM, Samulowitz U, Vollmer J, Uhlmann E, Jurk M, Lipford G;
PI Rankin R;
XX
DR WPI; 2004-257200/24.
XX
PT New immunostimulatory nucleic acid molecule having pyrimidine-purine
PT dinucleotide and a chimeric backbone, useful in treating and preventing
PT asthma, allergy, cancer, infectious disease, autoimmune disease or airway
PT remodeling.
XX
PS Example 10; SEQ ID NO 270; 276pp; English.
XX
CC The invention relates to an immunostimulatory nucleic acid molecule
CC comprising an internal pyrimidine-purine (YZ) dinucleotide and chimeric
CC backbone, where one internal YZ dinucleotide has a phosphodiester(-like)
CC internucleotide linkage, where optionally each additional internal YZ
CC dinucleotide has a phosphodiester(-like) or stabilised internucleotide
CC linkage, where other internucleotide linkages are stabilised. The
CC oligonucleotide is useful in stimulating or modulating an immune
CC response. The medicament shifts the immune response to a Th1 biased
CC response from a Th2 biased response. The oligonucleotide is also useful
CC in the manufacture of a medicament for treating asthma, allergy, cancer,
CC infectious disease, autoimmune disease, airway remodeling or chronic
CC obstructive pulmonary disease or in treating a subject who is a smoker or
CC who is free of symptoms of asthma. The oligonucleotide is useful in
CC inducing cytokine expression, e.g. IL-6 (interleukin-6), TNFalpha (tumour
CC necrosis factor alpha), IFNalpha (interferon-alpha), IFNgamma (interferon
CC -gamma) and IP-10 (interferon inducible protein). The oligonucleotide is
CC also useful in treating and preventing infections caused by viruses,
CC bacteria and parasites. The present sequence represents an
CC immunostimulatory nucleic acid.
XX
SQ Sequence 24 BP; 0 A; 6 C; 6 G; 12 T; 0 U; 0 Other;

Query Match 100.0%; Score 24; DB 12; Length 24;
Best Local Similarity 100.0%; Pred. No. 0.74;
Matches 24; Conservative 0; Mismatches 0; Indels 0; Gaps 0;

Qy 1 TCGTCGTTTCGTCGTTTCGTCGTT 24
||||||||||||||||||||||||
Db 1 TCGTCGTTTCGTCGTTTCGTCGTT 24

RESULT 5
ABQ18198
ID ABQ18198 standard; DNA; 619 BP.
XX
AC ABQ18198;
XX
DT 12-JUL-2002 (first entry)
XX
DE Oligonucleotide for detecting cytosine methylation SEQ ID NO 4789.
XX
KW Human; cytosine methylation; 5'-CpG-3'; uracil; cytosine; diagnosis;
KW drug; side effect; cancer; central nervous system; cardiovascular;
KW gastrointestinal; respiratory system; single nucleotide polymorphism;
KW SNP; cell differentiation; ds.
XX
OS Homo sapiens.
XX
PN WO200218632-A2.
XX
PD 07-MAR-2002.
XX
PF 01-SEP-2001; 2001WO-EP010074.
XX
PR 01-SEP-2000; 2000DE-01043826.
PR 05-SEP-2000; 2000DE-01044543.
XX
PA (EPIG-) EPIGENOMICS AG.
XX
PI Olek A, Piepenbrock C, Berlin K, Guetig D;
XX
DR WPI; 2002-371829/40.
XX
PT Determining the degree of cytosine methylation in genomic DNA, useful for
PT diagnosis and prognosis, comprises selective hybridization of amplicons
PT from chemically treated DNA.
XX
PS Claim 12; 56pp + Sequence Listing; 56pp; German.

Please mail w/ Office Action.

XX
CC This invention describes a novel method for determining the degree of
CC methylation of a particular cytosine in a motif 5'-CpG-3', present in a
CC genomic sample of DNA. The sample is treated chemically to convert
CC cytosine (C) but not methylated C, to uracil; then part of the genomic
CC DNA that contains the target C is amplified to form a labeled amplicon.
CC The amplicon is hybridised to two classes, each with at least one member,
CC of oligonucleotides and/or peptide-nucleic acid (PNA) oligomers and the
CC degree of hybridisation to both classes is determined from the label on
CC the amplicon. From the ratio of labels hybridised to the two classes of
CC oligomers, the degree of methylation is calculated. The method is used:
CC (i) for diagnosis and/or prognosis of side effects of therapeutic drugs
CC and of a wide range of diseases, e.g. cancer, disorders of the central
CC nervous, cardiovascular, gastrointestinal and respiratory systems etc.,
CC particularly by detecting mutations or single nucleotide polymorphisms
CC (SNP's); and (ii) for differentiation of cell or tissue types and for
CC investigating cell differentiation. The method allows the methylation
CC status of many C residues to be determined simultaneously. ABQ13410-
CC ABQ54121 represent genomic DNA sequences used to illustrate the method
CC for determining the degree of cytosine methylation described in the
CC disclosure of the invention
XX
SQ Sequence 619 BP; 69 A; 66 C; 167 G; 317 T; 0 U; 0 Other;

Query Match 100.0%; Score 24; DB 6; Length 619;
Best Local Similarity 100.0%; Pred. No. 0.71;
Matches 24; Conservative 0; Mismatches 0; Indels 0; Gaps 0;

Qy 1 TCGTCGTTTCGTCGTTTCGTCGTT 24
||||||||||||||||||||||||
Db 344 TCGTCGTTTCGTCGTTTCGTCGTT 367

RESULT 6
ABQ18199/c
ID ABQ18199 standard; DNA; 619 BP.
XX
AC ABQ18199;
XX
DT 12-JUL-2002 (first entry)
XX
DE Oligonucleotide for detecting cytosine methylation SEQ ID NO 4790.
XX
KW Human; cytosine methylation; 5'-CpG-3'; uracil; cytosine; diagnosis;
KW drug; side effect; cancer; central nervous system; cardiovascular;
KW gastrointestinal; respiratory system; single nucleotide polymorphism;
KW SNP; cell differentiation; ds.
XX
OS Homo sapiens.
XX
PN WO200218632-A2.
XX
PD 07-MAR-2002.
XX
PF 01-SEP-2001; 2001WO-EP010074.
XX
PR 01-SEP-2000; 2000DE-01043826.
PR 05-SEP-2000; 2000DE-01044543.
XX
PA (EPIG-) EPIGENOMICS AG.
XX
PI Olek A, Piepenbrock C, Berlin K, Guetig D;
XX
DR WPI; 2002-371829/40.
XX
PT Determining the degree of cytosine methylation in genomic DNA, useful for
PT diagnosis and prognosis, comprises selective hybridization of amplicons
PT from chemically treated DNA.
XX
PS Claim 12; 56pp + Sequence Listing; 56pp; German.
XX
CC This invention describes a novel method for determining the degree of
CC methylation of a particular cytosine in a motif 5'-CpG-3', present in a
CC genomic sample of DNA. The sample is treated chemically to convert
CC cytosine (C) but not methylated C, to uracil, then part of the genomic
CC DNA that contains the target C is amplified to form a labeled amplicon.
CC The amplicon is hybridised to two classes, each with at least one member,
CC of oligonucleotides and/or peptide-nucleic acid (PNA) oligomers and the
CC degree of hybridisation to both classes is determined from the label on
CC the amplicon. From the ratio of labels hybridised to the two classes of
CC oligomers, the degree of methylation is calculated. The method is used:
CC (i) for diagnosis and/or prognosis of side effects of therapeutic drugs
CC and of a wide range of diseases, e.g. cancer, disorders of the central
CC nervous, cardiovascular, gastrointestinal and respiratory systems etc.,
CC particularly by detecting mutations or single nucleotide polymorphisms
CC (SNP's); and (ii) for differentiation of cell or tissue types and for
CC investigating cell differentiation. The method allows the methylation
CC status of many C residues to be determined simultaneously. ABQ13410-
CC ABQ54121 represent genomic DNA sequences used to illustrate the method
CC for determining the degree of cytosine methylation described in the
CC disclosure of the invention
XX
SQ Sequence 619 BP; 317 A; 167 C; 66 G; 69 T; 0 U; 0 Other;

Query Match 100.0%; Score 24; DB 6; Length 619;
Best Local Similarity 100.0%; Pred. No. 0.71;
Matches 24; Conservative 0; Mismatches 0; Indels 0; Gaps 0;

Qy 1 TCGTCGTTTCGTCGTTTCGTCGTT 24
||||||||||||||||||||||||
Db 276 TCGTCGTTTCGTCGTTTCGTCGTT 253

RESULT 7
ABQ33259/c
ID ABQ33259 standard; DNA; 734 BP.
XX
AC ABQ33259;
XX
DT 12-JUL-2002 (first entry)
XX
DE Oligonucleotide for detecting cytosine methylation SEQ ID NO 19850.
XX
KW Human; cytosine methylation; 5'-CpG-3'; uracil; cytosine; diagnosis;
KW drug; side effect; cancer; central nervous system; cardiovascular;
KW gastrointestinal; respiratory system; single nucleotide polymorphism;
KW SNP; cell differentiation; ds.
XX
OS Homo sapiens.
XX
PN WO200218632-A2.
XX
PD 07-MAR-2002.
XX
PF 01-SEP-2001; 2001WO-EP010074.
XX
PR 01-SEP-2000; 2000DE-01043826.
PR 05-SEP-2000; 2000DE-01044543.
XX
PA (EPIG-) EPIGENOMICS AG.
XX
PI Olek A, Piepenbrock C, Berlin K, Guetig D;
XX
DR WPI; 2002-371829/40.
XX
PT Determining the degree of cytosine methylation in genomic DNA, useful for
PT diagnosis and prognosis, comprises selective hybridization of amplicons
PT from chemically treated DNA.
XX
PS Claim 12; 56pp + Sequence Listing; 56pp; German.
XX
CC This invention describes a novel method for determining the degree of
CC methylation of a particular cytosine in a motif 5'-CpG-3', present in a
CC genomic sample of DNA. The sample is treated chemically to convert
CC cytosine (C) but not methylated C, to uracil, then part of the genomic
CC DNA that contains the target C is amplified to form a labeled amplicon.

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CC The amplicon is hybridised to two classes, each with at least one member,
CC of oligonucleotides and/or peptide-nucleic acid (PNA) oligomers and the
CC degree of hybridisation to both classes is determined from the label on
CC the amplicon. From the ratio of labels hybridised to the two classes of
CC oligomers, the degree of methylation is calculated. The method is used:
CC (i) for diagnosis and/or prognosis of side effects of therapeutic drugs
CC and of a wide range of diseases, e.g. cancer, disorders of the central
CC nervous, cardiovascular, gastrointestinal and respiratory systems etc.,
CC particularly by detecting mutations or single nucleotide polymorphisms
CC (SNP's); and (ii) for differentiation of cell or tissue types and for
CC investigating cell differentiation. The method allows the methylation
CC status of many C residues to be determined simultaneously. ABQ13410-
CC ABQ54121 represent genomic DNA sequences used to illustrate the method
CC for determining the degree of cytosine methylation described in the
CC disclosure of the invention
XX
SQ Sequence 734 BP; 297 A; 250 C; 102 G; 85 T; 0 U; 0 Other;

Query Match 100.0%; Score 24; DB 6; Length 734;
Best Local Similarity 100.0%; Pred. No. 0.71;
Matches 24; Conservative 0; Mismatches 0; Indels 0; Gaps 0;

Qy 1 TCGTCGTTTCGTCGTTTCGTCGTT 24
||||||||||||||||||||||||
Db 515 TCGTCGTTTCGTCGTTTCGTCGTT 492

RESULT 8
ABQ33258
ID ABQ33258 standard; DNA; 734 BP.
XX
AC ABQ33258;
XX
DT 12-JUL-2002 (first entry)
XX
DE Oligonucleotide for detecting cytosine methylation SEQ ID NO 19849.
XX
KW Human; cytosine methylation; 5'-CpG-3'; uracil; cytosine; diagnosis;
KW drug; side effect; cancer; central nervous system; cardiovascular;
KW gastrointestinal; respiratory system; single nucleotide polymorphism;
KW SNP; cell differentiation; ds.
XX
OS Homo sapiens.
XX
PN WO200218632-A2.
XX
PD 07-MAR-2002.
XX
PF 01-SEP-2001; 2001WO-EP010074.
XX
PR 01-SEP-2000; 2000DE-01043826.
PR 05-SEP-2000; 2000DE-01044543.
XX
PA (EPIG-) EPIGENOMICS AG.
XX
PI Olek A, Piepenbrock C, Berlin K, Guetig D;
XX
DR WPI; 2002-371829/40.
XX
PT Determining the degree of cytosine methylation in genomic DNA, useful for
PT diagnosis and prognosis, comprises selective hybridization of amplicons
PT from chemically treated DNA.
XX
PS Claim 12; 56pp + Sequence Listing; 56pp; German.
XX
CC This invention describes a novel method for determining the degree of
CC methylation of a particular cytosine in a motif 5'-CpG-3', present in a
CC genomic sample of DNA. The sample is treated chemically to convert
CC cytosine (C) but not methylated C, to uracil, then part of the genomic
CC DNA that contains the target C is amplified to form a labeled amplicon.
CC The amplicon is hybridised to two classes, each with at least one member,
CC of oligonucleotides and/or peptide-nucleic acid (PNA) oligomers and the
CC degree of hybridisation to both classes is determined from the label on
CC the amplicon. From the ratio of labels hybridised to the two classes of
CC oligomers, the degree of methylation is calculated. The method is used:
CC (i) for diagnosis and/or prognosis of side effects of therapeutic drugs
CC and of a wide range of diseases, e.g. cancer, disorders of the central
CC nervous, cardiovascular, gastrointestinal and respiratory systems etc.,
CC particularly by detecting mutations or single nucleotide polymorphisms
CC (SNP's); and (ii) for differentiation of cell or tissue types and for
CC investigating cell differentiation. The method allows the methylation
CC status of many C residues to be determined simultaneously. ABQ13410-
CC ABQ54121 represent genomic DNA sequences used to illustrate the method
CC for determining the degree of cytosine methylation described in the
CC disclosure of the invention
XX
SQ Sequence 734 BP; 85 A; 102 C; 250 G; 297 T; 0 U; 0 Other;

Query Match 100.0%; Score 24; DB 6; Length 734;
Best Local Similarity 100.0%; Pred. No. 0.71;
Matches 24; Conservative 0; Mismatches 0; Indels 0; Gaps 0;

Qy 1 TCGTCGTTTCGTCGTTTCGTCGTT 24
||||||||||||||||||||||||
Db 220 TCGTCGTTTCGTCGTTTCGTCGTT 243

RESULT 9
ABK28370
ID ABK28370 standard; DNA; 6167 BP.
XX
AC ABK28370;
XX
DT 23-APR-2002 (first entry)
XX
DE DNA transcription associated complementary genomic DNA #122.
XX
KW DNA transcription associated gene; peptide nucleic acid; PNA-oligomer;
KW PNA; cytosine methylation state; SNP; retroviral infection; gene; ds;
KW single nucleotide polymorphism; adenosine deaminase deficiency; cancer;
KW viral infection; Sezary syndrome; haematological disorder; tuberculosis;
KW immunological disorder; Werner syndrome; developmental disorder;
KW psoriasis; Rieger's syndrome; neurological disorder; erythropoiesis;
KW neurodegenerative disorder; Waardenburg syndrome; Niemann-Pick disease;
KW myelodysplastic syndrome; myocardial infarction; hypertension; arthritis;
KW angiogenesis; congenital heart disease; HDR syndrome; gene therapy;
KW polyglutamine disorder; solid tumour.
XX
OS Unidentified.
XX
PN WO200192565-A2.
XX
PD 06-DEC-2001.
XX
PF 06-APR-2001; 2001WO-EP003973.
XX
PR 06-APR-2000; 2000DE-01019058.
PR 07-APR-2000; 2000DE-01019173.
PR 30-JUN-2000; 2000DE-01032529.
PR 01-SEP-2000; 2000DE-01043826.
XX
PA (EPIG-) EPIGENOMICS AG.
XX
PI Olek A, Piepenbrock C, Berlin K;
XX
DR WPI; 2002-090046/12.
XX
PT New nucleic acids or oligomers, useful for diagnosing or treating
PT diseases associated with DNA transcription, e.g. immunological disorders,
PT Werner syndrome, psoriasis, myocardial infarction, solid tumors or
PT cancer.
XX
PS Claim 1; SEQ ID NO 244; 32pp; English.
XX
CC The invention relates to a nucleic acid, which comprises a segment of the
CC chemically pretreated DNA of genes associated with DNA transcription from

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CC one of 346 sequences, and an oligomer, in particular an oligonucleotide
CC or peptide nucleic acid (PNA)-oligomer that hybridises to or is identical
CC to the chemically pretreated DNA of genes associated with DNA
CC transcription. The set of oligomer probes are useful for detecting the
CC cytosine methylation state and/or single nucleotide polymorphisms (SNPs)
CC in a chemically pretreated genomic DNA. The nucleic acids are useful for
CC diagnosing or treating diseases associated with DNA transcription
CC (particularly with the methylation status), e.g. adenosine deaminase
CC deficiency, viral infection, retroviral infection, Sezary syndrome,
CC haematological disorders, immunological disorders, Werner syndrome,
CC tuberculosis, developmental disorders, psoriasis, Rieger's syndrome,
CC neurological disorders, neurodegenerative disorders, Waardenburg
CC syndrome, Niemann-Pick disease, myelodysplastic syndrome, myocardial
CC infarction, hypertension, angiogenesis, erythropoiesis, congenital heart
CC disease, HDR syndrome, arthritis, polyglutamine disorders, solid tumours
CC or cancer. Sequences ABK28127-ABK28472 represent DNA transcription
CC associated genomic DNA molecules of the invention. Note: The sequence
CC data for this patent did not form part of the printed specification but
CC was obtained in electronic format directly from the European Patent
CC Office

SQ Sequence 6167 BP; 1658 A; 282 C; 1483 G; 2741 T; 0 U; 3 Other;

Query Match 100.0%; Score 24; DB 6; Length 6167;
Best Local Similarity 100.0%; Pred. No. 0.7;
Matches 24; Conservative 0; Mismatches 0; Indels 0; Gaps 0;

Qy 1 TCGTCGTTTCGTCGTTTCGTCGTT 24
||||||||||||||||||||||||
Db 760 TCGTCGTTTCGTCGTTTCGTCGTT 783

RESULT 10
ADI16076
ID ADI16076 standard; DNA; 23 BP.
XX
AC ADI16076;
XX
DT 22-APR-2004 (first entry)
XX
DE Immunostimulatory oligodeoxynucleotide SEQ ID NO:7.
XX
KW ds; immunostimulatory; antibacterial; antiallergic; antiasthmatic;
KW cytostatic; virucide; fungicide; antiparasitic; interleukin antagonist;
KW gene therapy; infectious disease; allergy; asthma; cancer.
XX
OS Unidentified.
XX
PN WO2004005476-A2.
XX
PD 15-JAN-2004.
XX
PF 03-JUL-2003; 2003WO-US021113.
XX
PR 03-JUL-2002; 2002US-0393880P.
PR 03-JUL-2002; 2002US-0394090P.
PR 03-JUL-2002; 2002US-0394091P.
PR 03-JUL-2002; 2002US-0394164P.
PR 03-JUL-2002; 2002US-0394193P.
XX
PA (COLE-) COLEY PHARM GROUP INC.
XX
PI Krieg AM;
XX
DR WPI; 2004-091353/09.
XX
PT New immunostimulatory nucleic acid molecule composition comprising CpG
PT motifs, useful for diagnosing, preventing and/or treating infectious
PT diseases, allergies, asthma and cancers.
XX
PS Disclosure; SEQ ID NO 7; 257pp; English.
XX
CC The invention relates to a novel composition comprising an
CC immunostimulatory nucleic acid molecule. A composition of the invention
CC has antibacterial, antiallergic, antiasthmatic, cytostatic, virucide,
CC fungicide, and antiparasitic activity. A composition may act as an
CC interleukin antagonist-4, or interleukin antagonist-5, and may have a use
CC in gene therapy. The methods and compositions of the present invention
CC are useful for diagnosing, preventing and/or treating infectious disease,
CC allergy, asthma, cancer, where the infectious disease is a herpes simplex
CC virus, bacterial, fungal or parasitic infection, and where the cancer is
CC a biliary tract cancer, bone cancer, brain and CNS cancer, breast cancer,
CC cervical cancer, choriocarcinoma, colon cancer, connective tissue cancer,
CC endometrial cancer, oesophageal cancer, eye cancer, gastric cancer,
CC Hodgkin's lymphoma, intraepithelial neoplasms, larynx cancer, lymphomas,
CC liver cancer, lung cancer (e.g. small cell and non-small cell), melanoma,
CC neuroblastomas, oral cavity cancer, ovarian cancer, pancreas cancer,
CC prostate cancer, rectal cancer, sarcomas, skin cancer, testicular cancer,
CC thyroid cancer and renal cancer. The present sequence represents an
CC immunostimulatory nucleic acid molecule of the invention.
XX
SQ Sequence 23 BP; 0 A; 6 C; 6 G; 11 T; 0 U; 0 Other;

Query Match 95.8%; Score 23; DB 12; Length 23;
Best Local Similarity 100.0%; Pred. No. 1.9;
Matches 23; Conservative 0; Mismatches 0; Indels 0; Gaps 0;

Qy 1 TCGTCGTTTCGTCGTTTCGTCGT 23
|||||||||||||||||||||||
Db 1 TCGTCGTTTCGTCGTTTCGTCGT 23

RESULT 11
ADI16081
ID ADI16081 standard; DNA; 23 BP.
XX
AC ADI16081;
XX
DT 22-APR-2004 (first entry)
XX
DE Immunostimulatory oligodeoxynucleotide SEQ ID NO:12.
XX
KW ds; immunostimulatory; antibacterial; antiallergic; antiasthmatic;
KW cytostatic; virucide; fungicide; antiparasitic; interleukin antagonist;
KW gene therapy; infectious disease; allergy; asthma; cancer.
XX
OS Unidentified.
XX
PN WO2004005476-A2.
XX
PD 15-JAN-2004.
XX
PF 03-JUL-2003; 2003WO-US021113.
XX
PR 03-JUL-2002; 2002US-0393880P.
PR 03-JUL-2002; 2002US-0394090P.
PR 03-JUL-2002; 2002US-0394091P.
PR 03-JUL-2002; 2002US-0394164P.
PR 03-JUL-2002; 2002US-0394193P.
XX
PA (COLE-) COLEY PHARM GROUP INC.
XX
PI Krieg AM;
XX
DR WPI; 2004-091353/09.
XX
PT New immunostimulatory nucleic acid molecule composition comprising CpG
PT motifs, useful for diagnosing, preventing and/or treating infectious
PT diseases, allergies, asthma and cancers.
XX
PS Disclosure; SEQ ID NO 12; 257pp; English.
XX
CC The invention relates to a novel composition comprising an
CC immunostimulatory nucleic acid molecule. A composition of the invention
CC has antibacterial, antiallergic, antiasthmatic, cytostatic, virucide,
CC fungicide, and antiparasitic activity. A composition may act as an